MAR 25 2003
PATENT & TRADEMARK OFFICE

16 F H

1639

CASE D0053 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Stephen C. D'Amico		3-21-03
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
TSUCHIHASHI ET AL.
APPLICATION NO: 10/005,956
FILED: NOVEMBER 30, 2001
FOR: HUMAN SINGLE NUCLEOTIDE POLYMORPHISMS

Assistant Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

Applicants believe this paper is being filed before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-3880.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

Some of the listed references were cited in a search report in a corresponding PCT International application. Copies of these references and the search report are enclosed herewith.

Also, copies of the other cited references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-5289

Stephen C. D'Amico
Agent for Applicants
Reg. No. 46,652

Date: 3-21-03

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

O I P E
MAR 2 5 2003
PATENT & TRADEMARK OFFICE
JC85

ATTY. DOCKET NO.
D0053 NP
APPLICATION NO.
10/005,956
APPLICANT
TSUCHIHASHI ET AL.
FILING DATE
NOVEMBER 30, 2001

Group

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AA	Kitamura et al. (1999) American Journal of Physiology 276:H1664-H1671
	AB	
	AC	
	AD	
	AE	
	AF	
	AG	
	AH	
	AI	
	AJ	
	AK	
	AL	
	AM	
	AN	

EXAMINER | **DATE CONSIDERED**

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
D0053 NP
APPLICATION NO.
10/005,956
APPLICANT
TSUCHIHASHI ET AL.
FILING DATE
NOVEMBER 30, 2001

Group

OIPE JC95 MAR 2 5 2003 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	WO9964626	12/16/99	PCT			☐	☐
	AN	WO9911799	3/11/99	PCT			☐	☐
	AO	WO0022166	4/20/00	PCT			☐	☐
	AP	WO9851822	11/19/98	PCT			☐	☐
	AQ	EP0955382A2	11/10/99	EP			☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Wang et al. (1998) Science 280:1077-1082
	AS	Rieder et al. (1998) Faseb Journal 12:A358
	AT	Mukae et al. (2000) Hypertension (Baltimore) 36:127-131

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

ABD 7/14/03 in MS

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

To:
BRISTOL-MYERS SQUIBB COMPANY
Attn. D'Amico, Stephen
P.O. Box 4000,
Lawrenceville-Princeton Road
Princeton, New Jersey 08543
UNITED STATES OF AMERICA

BMS PATENT LAW

NOT DKTD

MAR 05 2003

Docketed Item
Due Date
Attorney (SOH)

Applicant's or agent's file reference: D0053	Date of mailing (day/month/year): 19/02/2003
International application No.: PCT/US 01/47235	PAYMENT DUE within 45 ~~months~~/days from the above date of mailing
Applicant: BRISTOL-MYERS SQUIBB COMPANY	International filing date (day/month/year): 03/12/2001

DKTD — U.S. -105- 5/19/03

1. This International Searching Authority

(i) considers that there are 8 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

1-50 (all partially)

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

EUR 945,00	x	7	=	EUR 6.615,00
Fee per additional invention		number of additional inventions		total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [X] Claim(s) Nos. see add. sheet _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Barbara Klaver

Form PCT/ISA/206 (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Although claims 18-21, 23-26,28,29,44,45,47,48,49 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Claims Nos.: 2-9,14-16,17,20,21,25,32,33,38 and
10-13,26,27,29-31,34-36,39-42,45-47,49,50 partially;

Claims 2-9,14-16,17,20,21,25,32,33,38 all relate to the technical information of Table V which is not present in the description. The subject-matter of the respective claims could therefore only be searched with respect to a polymorphic position of Aminopeptidase P in general.

Claims 10-13,26,27,29-31,34-36,39-42,45-47,49,50 all relate to a polymorphic position of the human Aminopeptidase P which is not clearly specified. It is not apparent from the description, present Tables or the claims from where the numbering starts; a correct identification of the calimed polymorphic position is therefore not possible. Accordinly, the search was limited to a polymorphic position of the human Aminopeptidase P in general.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-50 partially

Isolated nucleic acid derived from a human gene encoding Aminopeptidase P protein (XPNPEP2), wherein said nucleic acid comprises at least one polymorphic position or is specified from Table V or is depicted in a nucleic acid sequence selected from the group consisting of SEQID163-288, SEQID643-SEQID706, SEQID910-961 or SEQID1574-1575; wherein the polymorphic position resides in a coding or non-coding position within the genomic sequence; wherein the polymorphic position is selected from 74651C or 74651T of the Aminopeptidase P genomic sequence and is at least 30-40 nucleotides in length; a hybridizing probe; a method of analyzing nucleic acid sample by determining the nucleic acid sequence at one or more polymorphic positions in gene encoding Aminopeptidase P protein (XPNPEP2); method of constructing haplotypes using said isolated nucleic acid and using said haplotype to identify an individual for the presence of a disease phenotype; method for identifying an individual at risk of developing a disorder upon administration of ACE inhibitor by determing the nucleotide present at one polymorphic position or amplifying sequences across one polymorphic position from an obtained sample and comparing said polymorphic position with a known data set; a library of nucleic acids which comprises one or more polymorphic positions within a gene encoding Aminopeptidase P protein (XPNPEP2); a kit for identifying an individual at risk of developing a disorder upon administration of ACE inhibitor and/or vasopeptidase inhibitor containing primers hybridizing to at least one polymorphic position in a gene encoding Aminopeptidase P protein (XPNPEP2); method of genotyping an individual and determing the nucleotide present at one polymorphic position from an obtained sample and comparing said polymorphic position with a known data set;

2. Claims: 1-9, 14-25, 28, 32,33,37,38,43,44,48 partially

Isolated nucleic acid derived from a human gene encoding Bradykinin receptor B1 protein (BDKRB1), wherein said nucleic acid comprises at least one polymorphic position or is specified from Table V or is depicted in a nucleic acid sequence selected from the group consisting of SEQID163-288, SEQID643-SEQID706, SEQID910-961 or SEQID1574-1575; wherein the polymorphic position resides in a coding or non-coding position within the genomic sequence; a hybridizing probe; a method of analyzing nucleic acid sample by determining the nucleic acid sequence at one or more polymorphic positions in gene encoding Bradykinin receptor B1 protein (BDKRB1); method of constructing haplotypes using said isolated nucleic acid and using said haplotype to identify an individual for the presence of a disease phenotype; method

for identifying an individual at risk of developing a disorder upon administration of ACE inhibitor by determing the nucleotide present at one polymorphic position or amplifying sequences across one polymorphic position from an obtained sample and comparing said polymorphic position with a known data set; a library of nucleic acids which comprises one or more polymorphic positions within a gene encoding Bradykinin receptor B1 protein (BDKRB1); a kit for identifying an individual at risk of developing a disorder upon administration of ACE inhibitor and/or vasopeptidase inhibitor containing primers hybridizing to at least one polymorphic position in a gene encoding Bradykinin receptor B1 protein (BDKRB1); method of genotyping an individual and determing the nucleotide present at one polymorphic position from an obtained sample and comparing said polymorphic position with a known data set;

3. Claims: 1-9, 14-25, 28, 32,33,37,38,43,44,48 partially

as invention 2, but limited to the Tachykinin receptor 1 protein (TACR1).

4. Claims: 1-9, 14-25, 28, 32,33,37,38,43,44,48 partially

as invention 2, but limited to the C1 esterase inhibitor protein (C1NH).

5. Claims: 1-50 partially

as invention 1, but limited to the Kallikrein 1 protein (KLK1) and wherein the polymorphic position is selected from 4627C or 4627T of the Kallikrein 1 protein genomic sequence and is at least 30-40 nucleotides in length.

6. Claims: 1-50 partially

as invention 1, but limited to the Bradykinin receptor B2 protein (BDKRB2) and wherein the polymorphic position is selected from 62738T or 62738A of the Bradykinin receptor B2 protein genomic sequence and is at least 30-40 nucleotides in length.

7. Claims: 1-9, 14-25, 28, 32,33,37,38,43,44,48 partially

as invention 2, but limited to the Angiotensin converting enzyme 2 protein (ACE2).

8. Claims: 1-9, 14-25, 28, 32,33,37,38,43,44,48 partially

as invention 2, but limited to the Protease inhibitor 4 (PI4).

REASONING FOR THE LACK OF UNITY OF THE INVENTION

Isolated human nucleotide sequences comprising at least one polymorphic position and encoding a polypeptide which is involved in hypertension-related disorders have already been disclosed in the prior art. See for example:

1. Mukae, S., et al.; Hypertension (July 2000), Vol. 36, No. 1, pp. 127-131; Single nucleotide polymorphisms of bradykinin B2 receptor promoter identified to be involved in ACE inhibitor-related cough.

2. Rieder, M.J., et al.; FASEB Journal, 17-03-1998, Vol. 12, No. 4, page A358; detection of single nucleotide polymorphisms in the angiotensin converting enzyme and development of a SNP map.

3. EP0955382, Affymetrix, Inc., 10.11.1999; detection of single nucleotide polymorphisms in 75 candidate genes having a role in hypertension, e.g. Bradykinin B2 receptor , Kallikrien, Angiotensin converting enzyme, see Table 1.

4. WO0022166, Eurona Medical AB, 20-04-2000; polymorphic positions determined within human genes related to cardiovascular stautus, e.g. ACE, AGT genes, ACE as marker for hypertension, bradykinin as ACE substrate, positions in regulatory and coding regions.

In the light of the prior art, the following problem and corresponding solutions can be identified.

1. Problem:

The provision of further hypertension-related polynucleotide sequences exhibiting at least one single nucleotide polymorphism.

1. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Aminopeptidase P protein (XPNPEP2).

2. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Bradykinin receptor B1 protein (BDKRB1).

3. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Tachykinin receptor 1 protein (TACR1).

4. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human C1 Esterase inhibitor protein (C1NH).

5. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Kallikrein 1 protein (KLK1).

6. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Bradykinin receptor B2 protein (BDKRB2).

7. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Angiotensin converting enzyme 2 protein (ACE2).

8. Solution:

Single nucleotide polymorphism (SNP) exhibiting polynucleotide sequence encoding the human Protease inhibitor 4 protein (PI4).

In view of the fact that isolated human nucleotide sequences comprising

at least one polymorphic position and encoding a polypeptide which is involved in hypertension-related disorders have already been disclosed in the prior art, due to the essential difference in function and primary structure of the polypeptides of the eight different solutions to the problem; and due to the fact that no other technical features can be distinguished which, in the light of the prior art could be regarded as special technical features, the ISA is of th eopinion that there is no single inventive concept underlying the plurality of claimed inventions of the current application within the sense of Rule 13.1 PCT.

COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/US 01/47235

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64626 A (GENOSTIC PHARMA LTD ;ROBERTS GARETH WYN (GB)) 16 December 1999 (1999-12-16) pages 2,6-7,37, examples 6,9, claims ---	1-50
Y	WO 99 11799 A (MEDICAL COLLEGE OF GEORGIA RES) 11 March 1999 (1999-03-11) page 7, line 4 - line 6 ---	1-50
Y	WANG D G ET AL: "Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 280, 1998, pages 1077-1082, XP002089398 ISSN: 0036-8075 the whole document --- -/--	1-50

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	RIEDER M J ET AL: "Development of a high resolution single nucleotide polymorphism map and haplo-type structure of the human angiotensin converting enzyme gene." FASEB JOURNAL, vol. 12, no. 4, 17 March 1998 (1998-03-17), page A358 XP001109595 Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part 1;San Francisco, California, USA; April 18-22, 1998 ISSN: 0892-6638 the whole document	
A	MUKAE SHUJI ET AL: "Bradykinin B2 receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough." HYPERTENSION (BALTIMORE), vol. 36, no. 1, July 2000 (2000-07), pages 127-131, XP002228956 ISSN: 0194-911X the whole document	
A	WO 00 22166 A (EURONA MEDICAL AB ;NORBERG LEIF TORBJORN (SE); JONSSON LENA (SE);) 20 April 2000 (2000-04-20) page 3,11, example 1	
A	EP 0 955 382 A (UNIV CASE WESTERN RESERVE ;AFFYMETRIX INC (US)) 10 November 1999 (1999-11-10) Table 1 + 3	
A	WO 98 51822 A (UNIV SOUTH CAROLINA) 19 November 1998 (1998-11-19) table 1	
A	KITAMURA SHIN-ICHI ET AL: "Effects of aminopeptidase P inhibition on kinin-mediated vasodepressor responses." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 276, no. 5 PART 2, May 1999 (1999-05), pages H1664-H1671, XP002228950 ISSN: 0002-9513	

2

Patent Family Annex

Information on patent family members

International Application No
PCT/US 01/47235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964626 A	16-12-1999	AU 4158699 A	30-12-1999
		EP 1084273 A1	21-03-2001
		WO 9964626 A2	16-12-1999
		GB 2339200 A ,B	19-01-2000
WO 9911799 A	11-03-1999	AU 9303498 A	22-03-1999
		WO 9911799 A2	11-03-1999
		US 6399349 B1	04-06-2002
WO 0022166 A	20-04-2000	AU 6116399 A	01-05-2000
		EP 1121462 A2	08-08-2001
		WO 0022166 A2	20-04-2000
		JP 2002527079 T	27-08-2002
		NO 20011847 A	14-06-2001
EP 0955382 A	10-11-1999	EP 0955382 A2	10-11-1999
		JP 2000032989 A	02-02-2000
WO 9851822 A	19-11-1998	US 5948616 A	07-09-1999
		AU 7486498 A	08-12-1998
		WO 9851822 A1	19-11-1998
		US 6376182 B1	23-04-2002